

IT IS CLAIMED:

1. A pharmaceutical composition effective in treating an inflammatory condition in mammalian subject, comprising a pharmaceutically effective dosage of an alpha-9

5 integrin antagonist compound and a pharmaceutical excipient.

2. The pharmaceutical composition of claim 1, wherein said inflammatory condition is characterized by increased neutrophil adhesion.

10 3. The pharmaceutical composition of claim 1, wherein said alpha-9 antagonist compound inhibits binding between alpha-9 integrin and an alpha-9 integrin ligand.

15 4. The pharmaceutical composition of claim 3, wherein said alpha-9 integrin antagonist compound exhibits a potency in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand that is at least 1/1000 as high an inhibitory potency exhibited by a compound selected from the group consisting of :

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,

SEARCHED
INDEXED
SERIALIZED
FILED

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy) phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

5

5. The pharmaceutical composition of claim 3, wherein said alpha-9 integrin antagonist compound is effective in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand as evidenced by an IC₅₀ for such inhibition of less than about 100 μM.

10

6. The pharmaceutical composition of claim 5, wherein said alpha-9 integrin antagonist compound is a selected from a group of compounds which inhibit alpha-4/beta-1 integrin binding to an alpha-4/beta-1 integrin ligand.

15

7. The pharmaceutical composition of claim 1, wherein said compound is selected from the group consisting of compounds having the formula:



20

R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

25

R² is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ can form a heterocyclic or a substituted heterocyclic group;

30

R³ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R² does not form a

SEARCHED
INDEXED
SERIALIZED
FILED
JULY 22 1998
RECEIVED
U.S. PATENT AND TRADEMARK OFFICE

heterocyclic group with R¹, R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ can form a heterocyclic or a substituted heterocyclic group;

R⁵ is -(CH₂)_x-Ar-R^{5'} where R^{5'} is selected from the group consisting of

5 -O-Z-NR⁸R^{8'} and -O-Z-R¹² wherein R⁸ and R^{8'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R⁸ and R^{8'} are joined to form a heterocycle or a substituted heterocycle, R¹² is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

10 -SO₂-,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

15 Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur; and pharmaceutically acceptable salts thereof.

8. The pharmaceutical composition of claim 1, wherein said alpha-9 integrin antagonist is selected from the group consisting of

20 N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

25 N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

SEARCHED
INDEXED
SERIALIZED
FILED

N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

9. A pharmaceutical composition for treating an inflammatory condition in a

10 mammalian subject, comprising

a pharmaceutical excipient; and

a small molecule compound selected for its ability to inhibit binding between alpha-9 integrin and an alpha-9 integrin ligand, as evidenced by said molecule exhibiting a potency in an alpha-9 integrin-alpha-9 integrin ligand binding assay that is at least 1/1000 as high as a potency of a compound selected from the group consisting of :

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

2007 FEB 27 2007 10:58 AM

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyl)oxy phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

5

10. The pharmaceutical composition of claim 9, wherein said compound is an inhibitor of alpha-4/beta-1 integrin binding to VCAM-1, as evidenced by its ability to inhibit said binding with a potency that is at least 1/1000 as high as a potency exhibited by a compound selected from the group consisting of:

10 N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyl)oxyphenylalanine,

15 N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyl)oxyphenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyl)oxyphenylalanine,

20 N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyl)oxyphenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyl)oxyphenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

25 N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyl)oxy phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

11. A method of screening for therapeutic compounds effective in treating an inflammatory condition, comprising

adding a test compound to an assay system which measures an amount of alpha-9 integrin binding to an alpha-9 integrin ligand, and

selecting the test compound as an effective therapeutic drug candidate, if said compound exhibits a binding inhibitory activity that is at least 1/1000 as potent as an activity exhibited by a compound selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethylthiaprolyl)-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethylthiaprolyl)-L-4-[3-(N,N-dimethylpropoxy)phenylalanine.

12. The method of claim 11, wherein said inflammatory condition includes increased neutrophil adhesion.

13. The method of claim 11, wherein said test compound is selected from a group of compounds that inhibit binding of alpha-4/beta-1 integrin to an alpha-4/beta-1 integrin ligand.

14. The method of claim 13, wherein said group of alpha-4/beta-1 integrin inhibitory compounds exhibit an inhibitory potency that is at least 1/1000 as high as an inhibitory potency exhibited by a compound selected from the group consisting of:

- 5 N-(toluene-4-sulfonyl)-L-proyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,
- 10 N-(toluene-4-sulfonyl)-L-proyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,
- 15 N-(1-methylpyrazole-4-sulfonyl)-L-proyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
- 20 N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethylthiaprolyl)-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
- 25 N-(toluene-4-sulfonyl)-N-methyl-L-alanyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
- 30 N-(toluene-4-sulfonyl)-L-[1,1-dioxo-thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
- 35 N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,
- 40 N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy)phenylalanine, and
- 45 N-(toluene-4-sulfonyl)-L-(5,5-dimethylthiaprolyl)-L-4-[3-(N,N-dimethylpropoxy]phenylalanine.

15. The method of claim 14, wherein said inhibition of binding of alpha-4/beta-1 integrin is measured in a test assay that measures binding of said alpha-4/beta-1 integrin molecule to VCAM-1.

16. The method of claim 13, wherein said test compound is selected from a group of carbamyl compounds having the formula: $R^1-SO_2-NR_2-CHR^3-Q-CHR^5-CO_2H$
wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

5 R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

10 R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R^2 does not form a heterocyclic group with R^1 , R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a heterocyclic or a substituted heterocyclic group;

15 R^5 is $-(\text{CH}_2)_x-\text{Ar}-R^5'$ where R^5' is selected from the group consisting of
 $-O-Z-NR^8R^{8'}$ and $-O-Z-R^{12}$ wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of $-\text{C}(\text{O})-$ and

$-\text{SO}_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

20 x is an integer of from 1 to 4;

25 Q is $-\text{C}(X)\text{NR}^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;
and pharmaceutically acceptable salts thereof.

17. The method of claim 11, wherein said alpha-9 integrin antagonist is selected from the group consisting of

- N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,
5 N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,
N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
10 N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethylthiaprolyl)-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
15 N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamoyloxy)phenylalanine,
N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and
N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy)
phenylalanine, and
20 N-(toluene-4-sulfonyl)-L-(5,5-dimethylthiaprolyl)-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

20 18. A method of treating an inflammatory condition in mammalian subject, comprising administering to the subject a pharmaceutically effective dosage of an alpha-9 integrin antagonist compound.

25 19. The method of claim 18, wherein said inflammatory condition is characterized by increased neutrophil adhesion.

30 20. The method of claim 18, wherein said alpha-9 integrin antagonist compound is a selected from a group of compounds which inhibit alpha-4/beta-1 integrin binding to an alpha-4/beta-1 integrin ligand.

21. The method of claim 18, wherein said alpha-9 integrin antagonist compound exhibits a potency in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand that is at least 1/1000 as high as an inhibitory potency exhibited
5 by a compound selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

10 N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

15 N-(toluene-4-sulfonyl)-N-methyl-L-alanyl-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[1,1-dioxo)thiamorpholin-3-carbonyl]-L-4(N,N-dimethylcarbamoyloxy)phenylalanine,

N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and

20 N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamoyloxy)

phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

22. The method of claim 18, wherein said compound is selected from the
25 group consisting of carbamyl compounds having the formula: $R^1-SO_2-NR_2-CHR^3-Q-$
 CHR^5-CO_2H

wherein

30 R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

R² is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ can form a heterocyclic or a substituted heterocyclic group;

R³ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R² does not form a heterocyclic group with R¹, R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ can form a heterocyclic or a substituted heterocyclic group;

R⁵ is -(CH₂)_x-Ar-R^{5'} where R^{5'} is selected from the group consisting of -O-Z-NR⁸R^{8'} and -O-Z-R¹² wherein R⁸ and R^{8'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R⁸ and R^{8'} are joined to form a heterocycle or a substituted heterocycle, R¹² is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

-SO₂-,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur; and pharmaceutically acceptable salts thereof.

23. The method of claim 18, wherein said alpha-9 integrin antagonist is selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

- N-(toluene-4-sulfonyl)-L-proyl-L-4-(N,N-dimethylcarbamylloxy)phenylalanine,
N-(1-methylpyrazole-4-sulfonyl)-L-proyl-L-4-(N,N-dimethylcarbamylloxy)phenylalanine,
5 N-(toluene-4-sulfonyl)-L-(1,1-dioxo-5,5-dimethylthiaprolyl)-L-4-(N,N-dimethylcarbamylloxy)phenylalanine,
N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamylloxy)phenylalanine,
10 N-(toluene-4-sulfonyl)-L-[1,1-dioxo]thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamylloxy)phenylalanine,
N-(N-p-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine, and
N-(N-p-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamylloxy)
phenylalanine, and
15 N-(toluene-4-sulfonyl)-L-(5,5-dimethylthiaprolyl)-L-4-[3-(N,N-dimethylpropoxy)phenylalanine.

PCT/EP2004/001750

Add C1
Add E6